To the extent to obviated by the above amendments, the Section 112, second paragraph, rejection of claims 10-15, are traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

With regard to the Examiner's concern over the expression "no mouse IL-3 activity", claim 10 now recites "as measured by inability to stimulate growth of Ba/F3 cells", as suggested by the Examiner at page 3 of the Office Action dated June 21, 2002. Thus, claim 10 is submitted to be definite.

The specification discloses at page 5, lines 5-13 that the hG-CSF and hG-CSF derivatives shown in Tables 1 and 2 can be used as the polypeptide having hG-CSF activity of the present invention. The amendments are believed to be supported by the specification and are not believed to add new matter.

Claim 11 relates to a fusion polypeptide having a spacer.

Withdrawal of the Section 112, second paragraph rejection is requested.

The Section 103 rejection of claims 10-15 over Curtis (U.S. Patent No. 5,073,627), Yamasaki (EP 0 335 423), de Sauvage (Nature 369:533-538) and Souza (U.S. Patent No. 4,999,291), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments, and the above.

The present invention relates to a polypeptide having two different activities, i.e., production and amplification of platelets, and production and amplification of neutrophils as disclosed at page 4, lines 11-16 in the specification.

c-mpl ligand used in the present invention has different activity from G-CSF. That is, c-mpl ligand has an activity of selectively increasing megakaryocytes which are platelet cells (see the expressed ratio of the expressed cells in Table 7), whereas the G-CSF has a strong activity of differentiating and proliferating neutrophils. As discussed at page 1, last line to page 2, line 2 in the specification, they are considered to have small overlapping activities.

The fusion protein of G-CSF and c-mpl-ligand having such different activities has a high activity of increasing leukocytes as shown in Table 8 of the present specification and a high activity of remarkably accelerating selective differentiation to megakaryocytes as shown in Table 7 (see the expressed ratio of CD61 expressed cells). It is apparent from these facts that the fusion polypeptide of the present invention has a ratio of inducing expression of CD61 expressed cells equal to or higher than c-mpl ligand alone, and has the ratio twice as great as G-CSF and c-mpl ligand in simultaneous combination use.

Herein, each of the references cited is reviewed. Curtis *et al.* teach that G-CSF and IL-3 are selected as a fusion polypeptide because they have considerable overlap in their broad range of biological activities. Actually, Curtis *et al.* disclose a fusion polypeptide in which G-CSF and IL-3 are linked and a fusion polypeptide in which G-CSF and IL-3 are linked via a spacer peptide. Furthermore, as pointed out by the Examiner, G-CSF and IL-3 have considerable overlap in their broad range of biological

activities (e.g., differentiation and proliferation of granulocytes). Accordingly, it is suggested that the activities of a fusion polypeptide of two polypeptides having similar activities would be equal to or higher than the case where the two polypeptides are simultaneously used in combination.

However, Curtis *et al.* neither disclose nor suggest the fusion protein of polypeptides having different activities, i.e., the fusion protein of hG-CSF and c-mpl ligand. Moreover, Curtis *et al.* neither disclose nor suggest what activity the fusion polypeptide of hG-CSF and m-mpl ligand have.

Yamasaki *et al.* disclose that PEG-modified G-CSF has increased stability in the blood. However, Yamasaki *et al.* neither disclose nor suggest the fusion polypeptide of hG-CSF and c-mpl ligand. Yamasaki *et al.* therefore fails to cure the deficiencies of Curtis *et al.*

de Sauvage *et al.* disclose that the activity of mpl is derived from the sequence of amino acids 1-153. However, de Sauvage *et al.* neither disclose nor suggest the fusion polypeptide of hG-CSF and c-mpl ligand. de Sauvage *et al.* therefore fails to cure the deficiencies of Curtis *et al.* and Yamasaki *et al.*

Souza discloses a process for the production of G-CSF using recombinant cells and combination use of G-CSF with other hematopoietic factors. However, Souza neither disclose nor suggest effects obtained by administration of the fusion

polypeptide. Souza fails to cure the deficiencies of any of Curtis *et al.*, Yamasaki *et al.* and de Sauvage *et al.*

As discussed above, each of the references cited neither discloses nor suggests the fusion polypeptide of hG-CSF and c-mpl ligand of the present invention and its effects. Whereas, the Examiner asserts that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the mpl ligand taught by de Sauvage *et al.* and the G-CSF analogue taught by Yamasaki *et al.* in the fusion protein taught by Curtis *et al.* to obtain a bifunctional hematopoietic protein. Furthermore the Examiner asserts that the ordinary artisan would have been motivated to obtain a polypeptide having two activities in view of Curtis' teachings that it is desirable to combine such activities, as well as by Souza's teaching of combining G-CSF activity with other hematopoietic factors, and therefore the ordinary artisan would have expected the resultant fusion protein to be at least as effective as the two cytokines administered together as a composition.

However, Applicants consider that, even if the above references are combined, the ordinary artisan would not have been motivated to combine two polypeptides having different activities to thereby obtain a polypeptide having two different activities at the same time. This is because the references cited neither disclose nor suggest that the fusion polypeptide having different activities, i.e., the fusion polypeptide of hG-CSF and c-mpl ligand, show both activities of hG-CSF and c-mpl at the same time and

additionally, the fusion polypeptide of hG-CSF and c-mpl remarkably accelerates the differentiation of megakaryocytic cells.

Thus, although the polypeptide of the present invention is a fusion polypeptide of polypeptides having different activities, each specific activity of the polypeptides can be obtained at a higher degree than the case where the polypeptides are separately used alone and the case where the polypeptides are simultaneously used in combination. These effects are neither disclosed nor suggested in the references cited, and cannot be expected by the ordinary artisan.

Consequently, the presently claimed invention could not have been easily expected, and the Section 103 rejection should be withdrawn.

In view of the above and attached, the claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Should the Examiner believe that an interview with the undersigned would facilitate allowance of this application, the Examiner is encouraged to contact the undersigned.

In re: Patent Application of YOKOI et al
Serial No. 09/680,514

Respectfully submitted,

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In re: Patent Application of YOKOI et al
Serial No. 09/680,514

MARKED-UP COPY OF AMENDED SPECIFICATION AND CLAIMS

IN THE SPECIFICATION:

Amend the specification as follows:

Page 1, delete the first paragraph and insert the following therefor:

--This is a continuation-in-part of application Serial No. 0[9]8/765,337, filed December 23, 1996, [now pending] abandoned, the entire content of which is hereby incorporated by reference in this application.

IN THE CLAIMS:

Amend the claims as follows:

10. (Amended) A fusion polypeptide which comprises a human granulocyte colony stimulating factor polypeptide and c-mpl ligand polypeptide [encoded by a nucleotide sequence selected from the nucleotide sequence SEQ ID NOS: 4, 6 and 8 wherein the fusion polypeptide] and has no mouse IL-3 activity as measured by inability to stimulate growth of Ba/F3 cells, wherein the polypeptide comprises the amino acid sequence shown in SEQ ID NO:1 or an amino acid sequence in which the amino acid nos. 155 to 327 of the amino acid sequence shown in SEQ ID NO:1 is replaced by an amino acid sequence

selected from an amino acid sequence represented in Table 1 and Table 2 a) to j) and l).

11. (Amended) The fusion polypeptide according to claim 10 in which the human granulocyte colony stimulating factor polypeptide is fused via a spacer peptide to [a] the c-mpl ligand polypeptide.

12. (Amended) The [A] fusion polypeptide [encoded by a nucleotide sequence selected from the nucleotide sequences shown in SEQ ID NOS: 4, 6 and 8] according to claim 11, wherein the polypeptide is selected from a polypeptide comprising the amino acid sequence shown in SEQ ID NO:2 or SEQ ID NO:3, an amino acid sequence in which the amino acid nos. 167 to 340 of the amino acid sequence shown in SEQ ID NO:2 is replaced by an amino acid sequence selected from the amino acid sequences represented in Table 1 and Table 2 a) to j) and l), and an amino acid sequence in which the amino acid nos. 171 to 344 of the amino acid sequence shown in SEQ ID NO: 3 is replaced by an amino acid sequence selected from the amino acid sequences represented in Table 1 and Table 2 a) to j) and l).